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TITLE: Measuring "Impossible" Intermolecular Cross-Peaks to Improve Selectivity and Specificity in Breast MRI

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Work in my laboratory at the time of grant submission had shown that intermolecular cross-peaks could be generated in vivo, and that these peaks gave enhanced contrast in rat brain images, including tumor enhancement. Work on this grant in the last period has focused on transitions to human subjects, signal enhancement, and demonstrations of contrast improvement. We have shown that we can take simultaneous, multislice images in humans with acceptable sensitivity at fields as low as 1.5T, the current clinical standard. We have also shown (in phantoms) that we can measure high-resolution localized MR spectra without suspectibility problems, which plague spectroscopic applications in breast tissue. Breast imaging sequences have been implemented on two MRI machines. Pulse sequence optimization for sensitivity and contrast enhancement in breast imaging is underway.

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Introduction

Work in my laboratory at the time of grant submission had shown that intermolecular cross-peaks could be generated in vivo, and that these peaks gave enhanced contrast in rat brain images, including tumor enhancement. These cross-peaks arise from dipolar couplings between distant spins in solution, which were previously thought to produce insignificant effects. Instead, we have shown (in five Science papers since 1993, among other places) that they lead to a completely new method for detecting small local variations in the resonance frequency. The overall goal of the research over the entire grant period is to demonstrate that we can enhance signal strength and specificity enough to make this a useful tool for clinical diagnosis of breast tumors. Work on this grant in the last period has focused on transitions to human subjects, signal enhancement, and demonstration of contrast improvement. We have shown that we can take simultaneous, multislice images in humans with acceptable sensitivity at fields as low as 1.5T, the current clinical standard. We have also shown (in phantoms) that we can measure high-resolution localized MR spectra without susceptibility problems, which plague spectroscopic applications in breast tissue. Breast imaging sequences have been implemented on two MRI machines. Pulse sequence optimization for sensitivity and contrast enhancement in breast imaging is underway.

Body

The Statement of Work from the original proposal, and progress towards the stated goals, is listed below.

Task 1: Characterize intermolecular zero-quantum coherences in samples with susceptibility variations *in vitro.*

a. Implement iZQC echo-planar imaging sequences on high resolution NMR spectrometers at Princeton (months 1-3)

b. Perform three-dimensional computer modeling of simple sequences on specific susceptibility distributions. (months 1-12)

c. Develop enhanced imaging sequences (multiple echoes, fat suppression) and test in phantoms and on normal and tumor-containing tissue samples (months 3-36)

Progress on these items:

a. We have implemented iZQC sequences on multiple NMR spectrometers at Princeton. At the time of the proposal, we viewed the existing spectrometers as our only option for doing phantom studies here. In the interim, a 3T head-only imager has been installed in the Psychology Department, and a 2T animal imager has been donated to my laboratory by Bracco Research. Both machines are currently being installed. In both cases, we will adapt existing sequences for use on these machines.

b. Three-dimensional modeling has been very successful in giving us more information about contrast from intermolecular zero-quantum and double-quantum imaging (see Figure 1). We have found that, in either case, the pulse sequences literally draw circles around regions with significant resonance frequency variation (as arises, for example, due to angiogenesis in tumors). The most recent extensions of this work have been submitted as a paper for the ISMRM meeting in April 2001.

c. Multiple-echo sequences have been developed theoretically which should enhance sensitivity by more than another factor of two. Sensitivity is now excellent for brain imaging (see below) and is becoming acceptable for breast imaging.

Task 2: Demonstrate breast MRI with contrast generated by intermolecular zero-quantum coherences

a. Program clinical scanner(s) at the University of Pennsylvania to do iZQC echo-planar imaging sequences at 4T and test on phantoms(months 1-3)

b. Include iZQC echo-planar studies in ongoing clinical protocols at the University of Pennsylvania on patients with known breast cancer at 4 Tesla (months 3-18)

c. Develop data base of iZQC images to compare with conventional MRI, mammograms and biopsy results; evaluate correlations with iZQC signal intensity, linewidth, and nonexponential behavior (months 3-18)

d. Evaluate advanced iZQC imaging sequences at 1.5 Tesla on phantoms (months 12-15)

e. Include iZQC echo-planar studies in ongoing clinical protocols at the University of Pennsylvania on patients with known breast cancer at 1.5 Tesla, and compare with conventional MRI (months 12-24)

Progress: a. Both 4T and 1.5T imagers at Penn have been programmed with a variety of advanced imaging sequences. These sequences have demonstrated high-speed, multislice imaging with spiral-k detection. The highest quality images to date are brain images; brain is an easier organ to start with, because fat suppression and susceptibility compensation are not necessary. The images in Figure 2 show that we get enhanced contrast and acceptable sensitivity at both 1.5T and 4T.

b. Work is ongoing to optimize pulse sequences for breast coils in use at UPenn. Issues here which are not faced in brain imaging include increased rf inhomogeneity, increased susceptibility variations, and instabilities due to breathing artifacts. All of these effects are automatically compensated in conventional images (Figure 3 shows an example of some of the 4T images we have taken); the trick is to achieve the same degree of compensation in iZQC/iDQC imaging, which means defeating the automatic routines normally used by the spectrometer. We have iZQC breast images at 4T, but the quality is not yet high enough for clinical use.

We have also demonstrated that we can do localized spectroscopy on phantoms with improved resolution (Figure 4). iZQCs fundamentally suppress susceptibility variations, which are very important linewidth contributions for breast MR because of the proximity of the lung. Breast studies have been attempted, but to date the signal jitter is too large for acceptable spectra, and we will be refining sequences to address this issue.

c. This work requires further progress on breast iZQC imaging, which we fully expect to demonstrate within the initially proposed time window.

d. Implementation of iZQC imaging at 1.5Tesla (the clinical standard) turned out to be easier than we expected, and we have already demonstrated it in brain.

e. Task planned for years 2-3

Task 3: Evaluate intermolecular multiple-quantum coherence contrast as a tool for breast cancer detection

a. As appropriate, test advanced pulse sequences on patients with no prior history of breast cancer and compare to other diagnostic methods (conventional MRI, mammography) (months 12-36).

Progress: task planned for years 2 and 3.

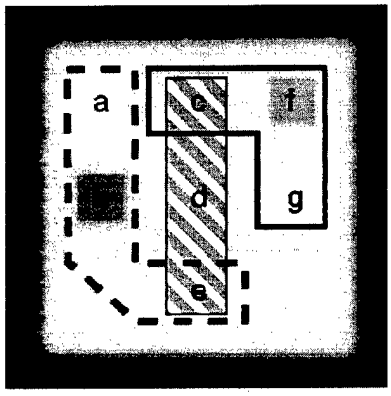

Figure 1. Above: 64 by 64 by 32 phantom used in iZQC imaging simulations. Each block *a*)-*g*) is an 8 by 8 by 8 embedded cube. Areas inside the dashed line have spin density variations (M_0), areas inside the solid line have T_2 variations, and the blocks under the striped box have a 25 Hz resonance offset. The background has a relative density of 0.5 and a T_2 of 100 ms. Area *a*) relative density 1, *b*) relative density 0.25, *c*) offset 25 Hz and T_2 50 ms, *d*) offset 25 Hz, e) offset 25 Hz and density 1, *f*) T_2 50 ms, and *g*) T_2 200 ms.

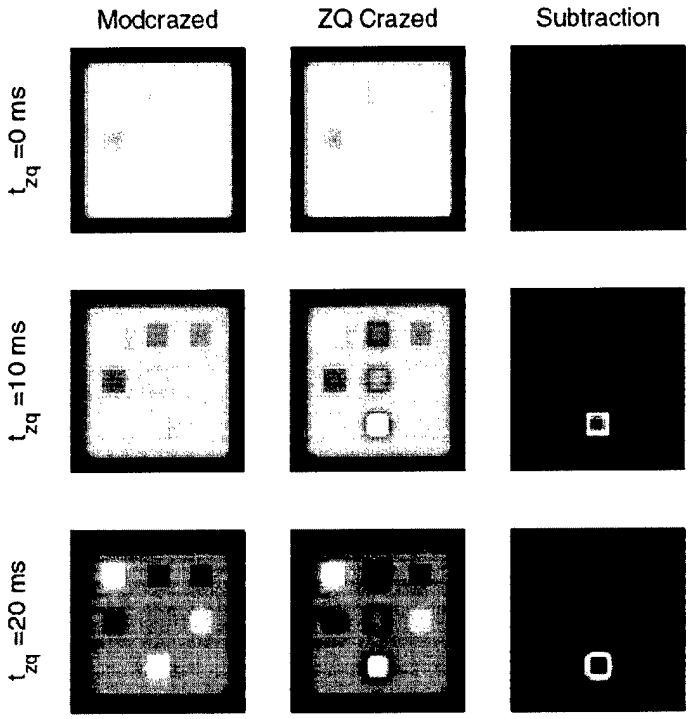

Figure 2. Comparison of contrast from iZQC imaging and a modified sequence (ModCRAZED, discussed in the next section) that includes an echo pulse during τ_{zq}. The difference highlights only regions with resonance frequency variations, as expected in and around tumors.

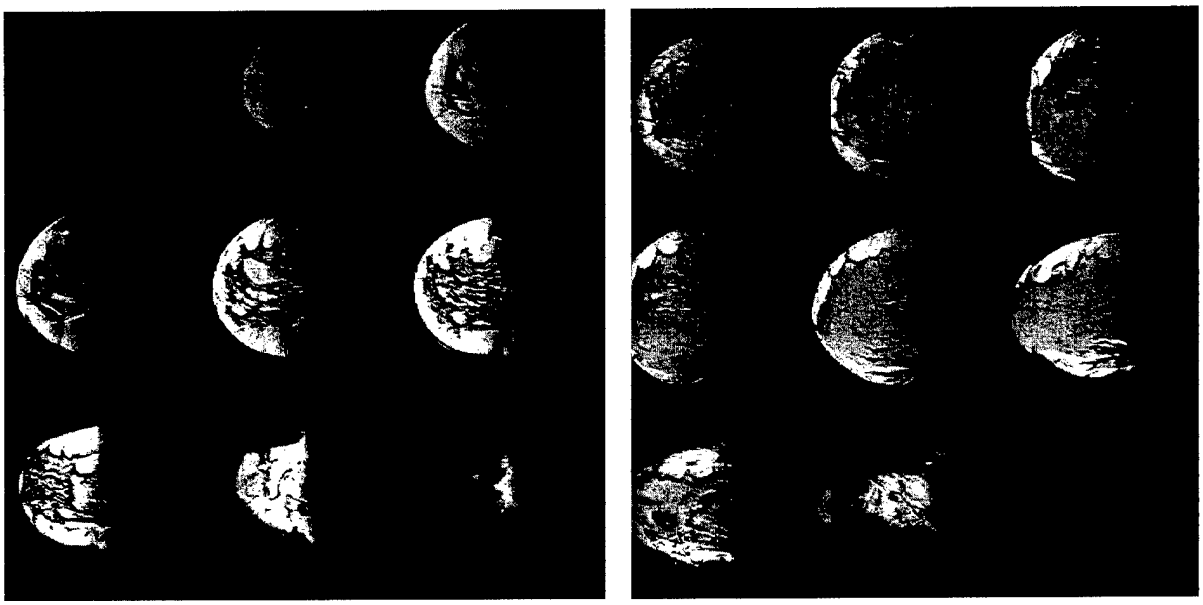

Figure 3. Sagittal, 4T breast images taken by Warren and coworkers as part of sequence optimization for iZQC imaging. These images are conventional MR images, showing the issues with fat-tissue variation and susceptibility changes to be addressed in iZQC imaging.

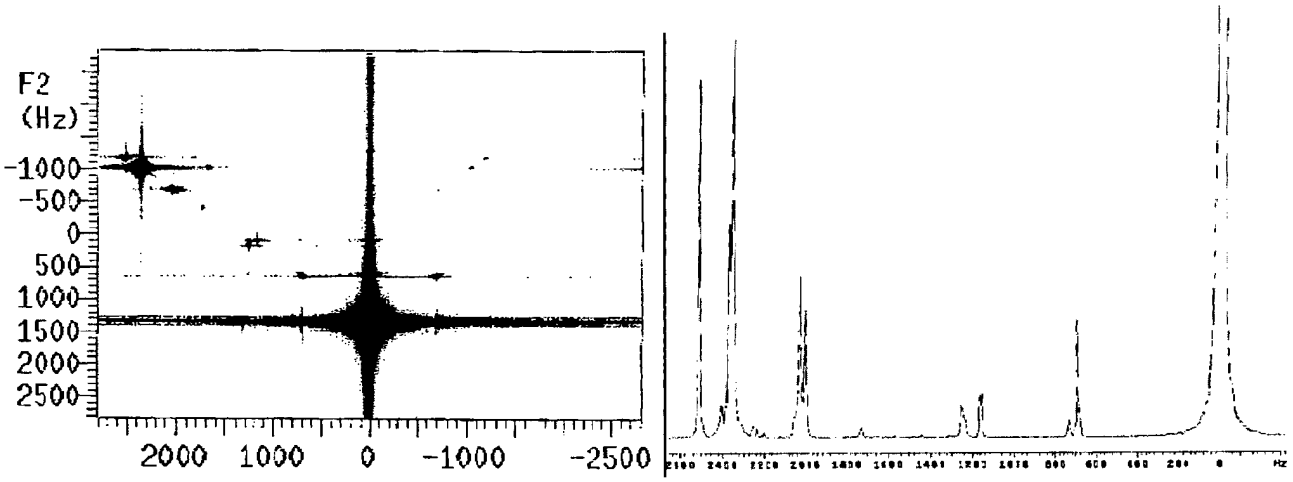

Figure 4. iZQC localized spectroscopy in a 5 cm benzene/olive oil phantom. Only the center 1 cm^3 is refocused by selective inversion pulses. The peaks in f_1 (horizontal) are all at difference frequencies between the solute and solvent. The spectrum on the right side is a trace along the pseudodiagonal ($f_1=f_2-f_{solvent}$). It has <5 Hz resolution (1024 points) and strong signal is still observed at the end of the indirectly detected FIDs. The shimmed lineshape over the entire phantom is about 30 Hz. Normal localization methods gave 1D spectra with lines about twice this wide and more distortion.

Key Research Accomplishments:

–Demonstrated human iZQC imaging with fast acquision (<5 min for four slices) and enhanced contrast

–Characterized advanced sequences for breast iZQC imaging

–Demonstrated localized spectroscopy with enhanced resolution.

Reportable Outcomes:

To date, three conference papers have been submitted or accepted dealing with the research done here. As these papers and subsequent papers are published, copies will be forwarded.

Conclusions:

We have clearly demonstrated that the novel contrast mechanism we proposed for breast MR can be extended to human studies, with acceptable data acquisition times and enhanced contrast. This progress has been significantly faster than we had expected. Work is ongoing to prove that these methods actually give better images in breast.

References:

None in this annual report